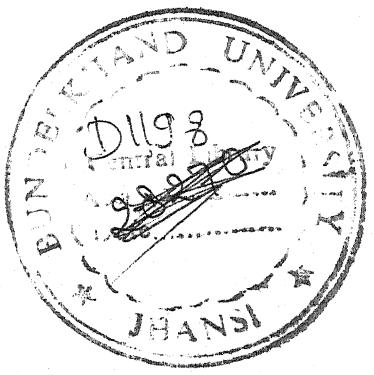
# CENTBUCRIDINE AS INTRAVENOUS REGIONAL ANALGESIC

THESIS
FOR
**DOCTOR OF MEDICINE**
( ANAESTHESIOLOGY )

BUNDELKHAND UNIVERSITY,
JHANSI (U. P.)



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# C E R T I F I C A T E

This is to certify that the research work entitled "CENTBUCRIDINE AS INTRAVENOUS REGIONAL ANALGESIC" which is being submitted as thesis for M.D. (Anaesthesiology) examination of Bundelkhand University, 1984 by Dr. Naresh Kumar Batra has been carried out in the Department of Anaesthesiology. He has put in the necessory stay in the department as per university regulations.

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## CERTIFICATE

Certified that the work entitled "CENTBUCRIDINE AS INTRAVENOUS REGIONAL ANALGESIC" has been carried out independently by Dr. N.K. Batra under our supervision and guidance. His observations have been regularly checked by us.

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# C O N T E N T S



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# INTRODUCTION

Pain is one of man's most compelling experience. It is an unpleasant sensation frequently associated with physical damage, therefore often described by the patients in connection with injury. Sherrington (1906), in his classical work on the central nervous system has defined pain as, "the psychical adjunct to an imperative protective reflex". This concept draws attention to the protective aspect of pain in preventing body injury from noxious stimuli. It is considered a signal from a warning device, but, like other expressions of the regulatory mechanisms within the body, it sometimes, functions in an unsatisfactory way. It is not only a distressing experience, but if continued, it may have harmful effects on the vital organs leading to impairment of function or even tissue damage (Wolff and Wolf, 1958).

The persistence of pain may interfere with the surgical procedures and make them very distressing for the patient and also more difficult for the surgeon. Hence its alleviation during surgery is, therefore, the raison d'etre of anaesthesia.

The endeavour of modern anaesthesiology stems around the attainment of ideal operating conditions (Co-operative and painfree patient) with the total body physiology maintained as near normal as possible. In order to hit the bull's eye, anaesthesiology today, is

armed with a number of drugs and techniques, which have some thing or other to boast their supremacy over the others, but still the eye could not be perforated.

General anaesthesia, although the most effective method of pain relief, is not without the risk of alterations in the cardiovascular and respiratory functioning, as also a definite change in body chemistry. These changes may not be of significance in normal patients but may have vital role to play in increasing the post-operative morbidity and mortality, in patients with metabolic and systemic disorders. With the suppression of reflexes the possibility of regurgitation and aspiration, under general anaesthesia, is also enhanced, particularly in patients with full stomach undergoing emergency surgery.

The absence of these limiting factors add a feather to the cap of local anaesthesia, thereby increasing its popularity under such circumstances. The discovery of a number of safe and potent local analgesic drugs, alongwith the evolution of various simple techniques of field blocks, has made them still more acceptable to the population as such.

One such technique, INTRAVENOUS REGIONAL ANALGESIA is a simple, effective, cheap and safe method of pain relief during surgery over limbs and can be repeated again and again. It claims special preference in busy hospitals and overworked emergencies where availability

of beds is a problem and rapid turnover of the patients, a must. Moreover most of the patients requiring emergency surgical intervention are not suitably prepared for an early general anaesthesia.

Almost a century has elapsed since local analgesic drug was injected intravenously by August Bier (1908) in 134 cases with no adverse effects. Several series were thereafter reported, but the technique got little attention. The credit for reintroducing intravenous regional analgesia in clinical practice goes to Holmes (1963), who suggested that lignocaine acted upon the motor and sensory nerve endings. He was ably supported by the studies of several workers, (Miles et al, 1964; Fleming et al, 1966, and Adriani, 1968). On the other hand Sorbie and Chacha (1965), concluded, on clinical and electrophysiological grounds, that the local anaesthetic acted mainly on the nerve trunks.

Various local analgesic drugs have been employed in this technique viz chloroprocaine, Lidocaine, Prilocaine and Bupivacaine etc. but an agent of choice which should provide wide margin of safety, rapid onset and longer duration of action is still at large. The occurrence of thrombophlebitis in subjects receiving choroprocaine may be due to its acidity and contraindicates its use. Prilocaine is less likely to produce signs of central nervous system toxicity than lidocaine and is equally

as effective as lidocaine but however it has the disadvantage of producing methaemoglobinaemia. Lidocaine is to be used with caution to avoid sensitivity reactions. Bupivacaine takes its own time to give full effect. Hence it can well be seen that every drug has one or the other limiting factor. Therefore under these circumstances the local analgesic, CENTBUCRIDINE, discovered at C.D.R.I. Lucknow, is employed in this technique to establish whether the drug is superior or not to the present conventional local analgesic drugs.

Have you proved the superiority of centbucridine in all the respects? Your conclusions are misleading.

# REVIEW OF LITERATURE

## REVIEW OF LITERATURE

The evolution of human race, although one of nature's most beautiful gift to the world, carries along with it one of its most dreadful curses and that is pain. Man is born in pain, lives in pain and dies in pain, it is therefore an experience never welcome. Since time immemorial, man has been fighting against it but, has not as yet been able to give it even a proper definition, what to talk of conquering it.

Pain has mostly been defined in the past in connection with its protective aspect in preventing the body injury by noxious stimuli. Leriche (1949) has stressed that on many occasions pain seems pointless and quite often the warning it affords is inadequate. As a symptom pain demands instant relief and is present in two out of every three patients seeking medical advice (Devine and Merskey, 1965).

The history of pain relief dates back to first recorded evidence of human civilisation, but enormous development of surgery during the nineteenth and twentieth centuries could well be possible as a result of commendable advancements, made by the anaesthesiologists in the field of pain relief.

Anaesthesia today, can broadly be classified as general and local anaesthesia, With regards to local

anaesthesia, endeavours have been made for a long time, but the major problems have largely been overcome comparatively recently. Much work is still being performed and more so required to improve the situation.

Modern local analgesia began with the introduction of cocaine in 1884 by Koller. Substitutes for the toxic cocaine soon came into being. Giesel's tropocaine appeared in 1891, Einhorn's novocaine (procaine) in 1899, Fourneau's stovaine in 1904. Meischer and Uhlmann introduced nupercaine in 1929, where as amethocaine appeared in 1931. The most commonly used local analgesic drug of the present day, lignocaine, was gifted by Lofgren and Lundquist to our profession in the year of 1943, but was put in clinical use by Gordh in 1948. Amongst the more recent local analgesic drugs, bupivacaine came into being in 1963 (Telivuo), while mepivacaine was synthesized in 1956 ( Ekenstam and Egner ).

Centbucridine is a new local analgesic drug, synthesized at C.D.R.I. Lucknow. Indian contribution to the family of currently available local analgesic drugs.

The first available account of intravenous administration of local analgesic is by Alms in 1886 (cited by Adams, 1944), who has shown that the intravenous injection of a local analgesic agent was associated with analgesia in the area supplied by that yessel, later

the method was applied to man by oppel and Goyanes (Allen 1914) and by Ransohoff(1910). The method is even occasionally mentioned today (Gevorkian 1962). But this knowledge was not put to practical use until, Bier(1908), published his account of venous anaesthesia for limb surgery. He had successfully given venous anaesthesia in about 30 cases. Many reports soon followed, Catz 1909, Hartel 1909, Hitzrot 1909 and Page & Mac donald 1909.

Bier's technique was described in detail by Adams,1944. Bier's technique though effective was cumbersome. An improvement in the form of a single tourniquet method was described by Morrison(1931). The subject was well reviewed by Adams(1944), but the credit for the reintroduction of the technique goes to Holmes(1963). His series consisted chiefly of relatively short operative procedures of a type suitable for the casualty department.

PREMEDICATION:-

Holmes(1963) believed that heavy premedication is benificial. On the other hand (Cox,J.M.R.(1964), had the opinion that for out patients, the distinct advantage of rapid recovery should not be offset by heavy premedication, Sadove, et al,(1952), were of the opinion that sedation usually by barbiturates renders the patients non-cooperative and the elicitation of analgesia becomes difficult. Moreover the cerebral cortex gets depressed and thus acts synergistically with lignocaine which also

depresses the brain.

TOURNIQUETS:-

An improvement in the form of single tourniquet was described by Morrison, 1931. Bell, et al, (1963), and Adams et al, (1964), have advocated the use of two tourniquet. Hoyle, J.R.(1965), introduced the use of two balloon cuffs. The upper balloon was inflated when the injection was being given while the second balloon inflated when the operation started. In this way tourniquet pain was abolished.

VENEPUNCTURE:-

Originally Bier had practiced cut down for the administration of drug and Morrison (1931) was first who suggested venepuncture and had made the technique more practicable. Holmes (1963), suggested that the site of injection whereever suitable, can be chosen distal to the tourniquet while Dawkins, et al,(1964), believed that it should be as near as possible, to the region of operation. Sorbie and Chacha (1965), were of the opinion that it should be in the distal part of thelimb i.e. near or distal to the wrist or ankle because valves in the proximal part of the veins are very powerful and withstand considerable pressure, so that the downward flow of solution is slow and incomplete. Sorbie and Chacha, found that the time taken by the drug to spread after a proximal injection was longer than after a

distal injection. Time of spread to the whole limb after a proximal injection was 5 minutes and 40 seconds, whereas it was 4 minutes and 50 seconds after distal injection. The site should not be very close to the tourniquet to avoid toxic reactions, as syringe pressure may exceed 300 torr and analgesic solution can enter the systemic circulation from below the inflated toruniquet. ( P. Prithvi Raj, et al, 1972).

EXSANGUINATION:-

Adams, et al, (1964), believed that exsanguination was of great importance for two reasons. Firstly the analgesic solution will be evenly distributed in the empty venous plexus and will also not be diluted by the blood present in the limb. Average blood volume in upper limb distal to the point of placement of the tourniquet was measured by Adams and Albert (1962), as 170ml. The concentration of 40 ml. lignocaine solution is much greater when 170 ml. of the blood is removed by elimination of this large dilution factor, as a result the analgesia would be even, complete and more prolonged. Secondly at the release of tourniquet there is no reservoir of blood containing drug ready to be dumped into the general circulation which may explain the lack of side effects in central nervous system as well as low blood levels of the drug determined chemically.

Exsanguination can be done by application of Esmarch's

bandage from fingers or toes upwards to reach the tourniquet (Holmes, 1963). But other authors (Dawkins, et al, 1964, and Cox, J.M.R., 1964), were of the opinion that gravitational drainage is good enough and there is no particular advantage claimed by using Esmarch's bandage and gravitational drainage is preferable where manipulation of the limb is painful. Holmes (1963), believed that the development of cutis marmorata leads to a reduction in the duration of anaesthesia. Bell, et al, (1963), concluded that the development of skin discolouration was not associated with the degree and duration of analgesia, but with the appearence of these signs the operator is virtually sure of the success of technique.

Colbern, E.C.(1970), emphasises the necessity of exsanguination with the view that it produces collapse of the vascular compartment of the extremity. Injection of anaesthetic solution into a full vascular compartment will impair complete and even distribution throughout the extremity and with the tourniquet inflated the vascular compartment is a closed space and relative collapse of the compartment is necessary to accept the injected solution. He also suggested that desired result of exsanguination can be hastened by a careful milking of the limb, disturbing any painful lesion as little as possible. Pneumatic splint is also described as an another alternative for exsanguination. (Dunbar, R.W.,Captain, M.C. and Mazze, R.I., 1967).

DOSE AND CONCENTRATION OF SOLUTION:-

Holmes (1963), advised the use of 200mgm of lignocaine solution for upper limb and upto 400 mgm for lower limb, in a concentration of .5%. Bell, et al, (1963), have found that with a dose of 3 mg/kg body weight mild neurological symptoms were present in half of their cases and that bradycardia and E.C.G. changes were often seen. These changes were not seen when the dose was reduced to half, but then analgesia was insufficient, unless limb ischaemia, produced by inflation of the tourniqet, was effected at least twenty minutes prior to the injection of drug. This modification would seem to make the method tedious and time consuming to the administrator and very unpleasant to the patient.

The use of dose as high as 800 mg of lignocaine solution in two cases is mentioned by Dawkins, et al, (1964). Adams, et al, used 40-50 ml of .5% solution i.e. 200 mg to 250 mg of the drug.

Kennedy, et al, (1965), advocated the use of an average of 182.5 mg of the lignocaine, with a maximum of 300 mg in .5% solution. Bromage and Robson,(1963), have defined the upper dose limit of lignocaine in healthy individuals, for the avoidence of toxicity, at .3 ml/lb body weight.

Dawkins, et al, (1964), have also used 20 ml. of 1% concentration instead of usual, .5% concentration.

Prilocaine is used in varying concentrations of .5% to 1% and dose ranging between 3 to 5 mg/kg. (Harris, W.H., 1969). However it is associated with the formation of methaemoglobinaemia and its use is restricted.

Chloroprocaine was used in doses ranging from 1 to 3 mg/kg in concentration of .25% to 1% with good results in 29 out of 38 volunteers. The incidence of thrombophlebitis was 8% in the series (Harris, W.H., Slater, E.M., 1965).

Bupivacaine was used by Moore, D.C. and Bridenbaugh, et al,(1971), for upper extrimity in .25% concentration, using 30-50 ml of solution. Rausso,M, Drexler. H. and Aronson, H.B.,(1981), have also employed bupivacaine in their series with this technique.

Suri, et al, (1983), are of the opinion that the effectiveness of the centbucridine is dose/concentration dependant. Using 40 ml. of .35% solution they could produce consistent sensory and motor blockade with minimum side effects for surgical anaesthesia. A lower concentration(.25%) however was not sufficient while higher (.5%) concentration although produced good blockade and long duration of action, but was associated with several side effects.

DIXON's LAW :-

It states that the concentration of a local analgesic solution required to block the sympathetic fibres in a mixed nerve is lower than that for the sensory fibres and that again is lower than the concentration for the motor fibres.

The concentration spreads more

in inflammed tissues due to increased capillary permeability. The effect is more first on the nerve terminals of smaller diameters than sympathetic fibre and those conducting pain impulses.

MODE OF ACTION:-

The mode of action of the intravenously injected local analgesic drugs still remains a ticklish problem. Various hypothesis have been put forward, but a concrete answer has yet to be achieved.

Bier (1908), used procaine hydrochloride with methylene blue into ischaemic limbs and noted the drug distribution in the tissues.

The drug diffuses slowly from the endothelium of the vessels into the tissues of the isolated limb. It is probably fixed to the nerve tissues and synapses and is stored in the tissue spaces. Not only the nerve trunk, but the nerve endings also get anaesthetised.

Distribution of the drug was studied by Shamay Cotev & Gordon. C, Robin, (1966), in dogs and Richard, B. Knapp and Myron Weinburg, (1969) by using lidocaine tagged with $C^{14}$ in adult monkeys. Levels of radioactivity after a determined time interval were obtained from specimen of extremity muscle, blood vessels and organs at autopsy. The anaesthetic solution was rapidly perfused throughout the tissues proximal to the site of injection and was held within the area bounded by

the tourniquet, untill release. Within 30 minutes after release it was found throughout the body tissues. The concentrations of the anaesthetic solution present intravascularly within the anaesthetised fore limb, did not diminish significantly over a period of 90 minutes, and therefore release of the toruniquet may allow a significant concentrations of the drug to suddenly enter systemic circulation. Symptoms of systemic toxicity on tourniquet release are possible even after 90 minutes following injection of a local anaesthetic solution.

De-V-Van Niekerk and Coetzee (1965) used radio opaque material to study the drug distribution. Fleming, S.A., Veiga. Pires, J.A. and Mc Cutcheon, R.M., (1966), used lignocaine containing hypaque and concluded that drug acts at tissue level on the nerve endings. Both motor and sensory nerve conduction have been measured in clinical (Adams, Dealey, Kenmore and Miles, et al, (1964), and experimental (Kenmore, et al, 1964) in intravenous regional analgesia and they found that conduction speed decreased from fifty two to forty two meters per second.

Recently a study was done by Dave, V.B., Ghate, S.V. and Rao, B. Venu prasad (1978), using radiocontrast material and found greater localization of the anaesthetic agent in the traumatized tissue.

There is a selective pick up of lignocaine by nerve

tissues as compared to other soft tissues (Shamay, Cotev and Gordon C.Robin, 1966). C $^{14}$ lebelled lignocaine was detected in axillary venous blood even before the release of the tourniquet. It is due to normal intra-osseous blood flow.

The effect of centbucridine on neuromuscular transmission is as follows as reported in the experimental work at C.D.R.I. The sciatic nerve anterior tibialis muscle preparation in chloralosed cats was used for this purpose. There was no effect of lignocaine in doses of 10 mg/kg/I/V and of centbucridine in dose of 2.5mg/kg/I/V. Closed intra arterial injection of 400 micrograms of centbucridine however produced 100% block, which developed slowly.

It is of interest to consider how analgesia and muscular paralysis occur, during intravenous regional analgesia. The paraesthesia suggests the possibility of a true nerve block, perhaps, produced by the perfusion of the veins of the nerves. The rapid onset and recovery however point to a more peripheral site of action, such as at the nerve endings. Obstruction or extensive destruction of venous system will prevent the development of satisfactory peripheral anaesthesia. The safty of the technique probably depends on the fixation of a major portion of the anaesthetic agent by the tissues. The amount of the drug fixed is higher when

exsanguination is efficient. Dispersion of the anaesthetic solution is most rapid and complete when a hand vein is used for injection then where a cubital vein is chosen as the retrograde flow of the solution is prevented by the competent valves. (Sorbie and Chacha, (1965).

Prithvi Raj, P., Garcia, C.E., Burleson, J.W. (1972) concluded in their work that lignocaine acts at the main nerve trunk to produce clinical anaesthesia after intravenous administration.

ANOXIA:-

Anoxia is also held responsible for the production of anaesthesia by lowering the $p^H$ in the limb and increased $PCo_2$ both of which are known to modify the membrane permeability or the low $p^H$ expediting or increasing the ionisation of lignocaine or through accumulation of metabolites e.g. lactic acid or by the direct compression of the nerve itself. In whatever way the occlusion and anoxia act, it was observed that once the anaesthesia had set in it lasted for considerable time, but the tourniquet starts producing discomfort after 40-50 minutes, in some cases. With this technique ischaemia may contribute to anaesthesia when 30 minutes have elapsed after application of the tourniquet. Anaesthesia of a limb from ischaemia alone has a different pattern of onset to that following drug injection and is considerably slower in development. When arm subjected to

total ischaemia, anaesthesia is not complete for 40 minutes. Sensation is first lost from finger tips and gradually the anaesthetic area extends more or less evenly up the arm. Motor power is lost in a similar way. Extensors being effected sooner than flexors. There is a difference in the pattern of nerve conduction loss in the ischaemic limb as compared with the anaesthetic limb as shown in the nerve conduction studies which confirm that anaesthesia is not due to ischaemia alone. It is probable however that as time passes the anaesthetic solution leaks through osseous veins into general circulation and anaesthesia is maintained to some extent by the ischaemia (Sorbie and Chacha, (1965).

PHARMACOKINETICS OF INTRAVENOUS REGIONAL ANALGESIA:-

The pharmacokinetic aspects of intravenous regional anaesthesia have been described by Tucker and Boas, 1971, they showed that after cuff release the peak plasma levels of lignocaine were 20 to 80 per cent lower than when the same dose of lignocaine was given by direct intravenous injection. The peak levels achieved were inversely proportional to the total time the tourniquet was applied and tended to be lower when the same dose was given by 0.5% rather than 1% solution. The release of lignocaine into the circulation was noted to be biphasic, with an initial fast release of about 30% of the dose, the remainder appearing by a gradual wash-out 50 percent of the dose of lignocaine can remain in the

arm 30 minutes after release of the cuff, so it is possible to re-establish anaesthesia within 10-30 minutes of the initial deflation of the tourniquet by reinflating and injecting half of the original dose of the drug.

INJECTION TOURNIQUET RELEASE TIME INTERVAL:-

Toxic reactions appear to be more common when the injection and tourniquet release time interval is less than 25 minutes, as observed by Bier (1908), who advocated an interval of 30 minutes, He suggested that no matter how short the surgical procedure, the tourniquet should not be released before 20 minutes, at least. Morrison, (1931), after experimental work on cats, recommended that minimum interval between the injection of drug and release of tourniqet should be 30 minutes. Adams, et al, (1964), thought that the negligible toxic reactions in their series were due to the long interval of one hour. In the series of Dawkins, et al, (1964), the interval was as low as 10 minutes but the dosage was also high and as such it is difficult to say as to which of the two factors were responsible for the incidence of toxic reactions.

Kennedy, et al, (1964), stress the importance of 25 minutes of injection tourniquet release interval to prevent toxic reactions. The smaller the dose and greater the injection release interval, the chances of toxic reactions are less.

Edwin.C. Colbern, (1970), suggests that tourniquet should not be deflated in a jerk, but it should be cycled to cut down on the bolus effect of the anaesthetic agent, as it is released into the general circulation. This is done by deflating the cuff for about 5 seconds then reinflating for about 45 seconds. The cycle is repeated 4-5 times and then the tourniquet is removed. Martin, G. Schiller (1976) also recommended the same.

EFFECT OF ANAESTHESIA:-

In a series of 30 cases conducted by Holmes (1963), there was complete analgesia in 21 cases. In 7 cases, patients noted some discomfort which was moderate and two cases failed owing to bad technique. Seventeen patients were fully satisfied with the method declaring it preferable to general anaesthesia, 8 patients commented about minor discomfort though they still felt that method was satisfactory, where as, four patients thought that general anaesthesia would have been better.

In the series of Bell, et al, (1963), 24 out of 26 cases had excellent analgesia while 2 failed.

Colbern, Edwin.C., (1970), had waiting period of 3-5 minutes in his series for complete analgesia and he proposed, should analgesia not be complete, a chaser dose of 5-10 ml. of normal saline solution be injected and this manoeuvre usually results in complete success as it forces further distribution of the anaesthetic agent.

Bells classification of degree of analgesia is as follows:

EXCELLENT:-

Lossof sensory, touch, pin prick and deep pressure, position sense, marked or total paralysis and no pain or discomfort from the operative procedure along with no tourniquet pain.

GOOD:-

Complete loss of touch, pain and position sensation but retained sensory response to maximum pressure when applied to the finger nail or toenail, interpretted as burning. Slight or no tourniquet pain. And motor paralysis little or none, when present it appeared late during operation.

FAIR:-

Incomplete anaesthesia, with mild pain or discomfort in reduction of a fracture. Severe or mild tourniquet pain. But no general anaesthesia was required.

POOR:-

Failure of anaesthesia

Reaction to tourniquet have also been classified by Mittal, N.K. , and Kackar, S.N., (1972) as-

WELL TOLERATED:-

When patient was comfortable and quiet.

TIGHTNESS:-

Patient felt tightnessin the limb but no supplementation was needed.

MILD DISCOMFORT:-

When patient complained of marked tightness, was restless but required no supplementation.

MARKED DISCOMFORT:-

When the patient constantly complained of tightness and required supplementation.

Dawkins, et al, (1964), in their series of 514 cases found excellent analgesia in 95% of cases. There was moderate analgesia in 3.5% and in the remainting 1.5% cases there was failure of analgesia.

Adams, et al, (1964), intheir series of 26 cases, conducted on upper limb exclusively, had complete analgesia in 25 cases.

Cox, J.M.R., (1964), reported complete analgesia in 36 patients in his series of 47 cases, moderate analgesia in 6 cases and poor response in 5 cases.

Kennedy, et al, (1965), gave intravenous regional analgesia to 77 patients and found complete analgesia in 75% and moderate in 12% cases. Fair in 10% and failed to achieve any analgesia in 3% of cases.

The most discouraging results were found in the work of Kennedy, et al, (1965), and the discredit to this technique was as a result of his observations.

Sorbie and Chacha (1965), intheir work on 128 cases found excellent result in 118 cases, moderate in 5 and had failure in 10 dases.

TOXIC REACTIONS:

Sadove, et al, (1952), have classified toxic reactions to local analgesic drugs as in normal individuals into

a- Central effect.

b- Peripheral effect.

In the central effect the stimulation of cerebral cortex and medullary centres was followed by depression and in the peripheral effect cardiovascular and respiratory systems were involved.

Moore and Bridenbaugh, (1960), believe that the bradycardia, associated with overdosage of local analgesic drugs is secondary to an initial tachycardia and to be caused by myocardial oxygen lack. This sequence of pulse rate change was not seen nor was there any other suggestion of hypoxaemia (Kennedy, et al, 1965). The bradycardia encountered in 15% of cases was attributed to medullary centre stimulation. E.C.G. signs of deteriorating cardiac activity were seen in 30% of cases described by Foldes, et al, (1960), in which acute toxicity experiments with lignocaine were carried out. Similar observations were described by Steinhaus, (1957), and by Stewart, et al, (1963). In the above series a variety of E.C.G. changes including S.T. segment depression, atrial and ventricular asystoles, nodal rhythum and sinus bradycardia were associated with release of the tourniquet, as was a fall in the systemic blood pressure in over 20% of the cases studied.

There seems to be several factors involved in the appearance of the toxic effects after the release of tourniquet. It would seem clear that, the most important causal factor is the dosage of the local analgesic agent employed. The other major factor responsible for the occurence of side effects with this technique, appears to be the injection tourniquet release interval. Sensitivity as opposed to overdosage is probably a very rare cause of toxicity manifestation which is encountered only with lignocaine.

Moore and Bridenbaugh, (1960), believed that, in less than 2% of cases, in which systemic symptoms arise after the administration of local analgesic drug, can a true allergy to the drug may be held responsible. de-Clive, Lowe., et al, (1958), used lignocaine in supplemental form during general anaesthesia in many thousand patients without a single case of drug sensitivity.

In the study of Foldes, F.F., Robert Molly and Mc Nall, P.G., et al, (1960), Procaine hydrochloride, 2-Chloroprocaine 1 mg. , Lidocaine .5% and tetracaine 0.5% hydrochloride, 0.125 mg. perkg. of body weight per minute were administered intravenously and chloroprocaine was shown to be the best tolerated and lidocaine the least well tolerated of the four compounds investigated.

Before this study the Centbucridine has not been used extensively as intravenous regional analgesic.

So reports on toxicity after intravenous route in human beings are available in only one series recently carried out by Suri, Y.V., Patnaik, G.K., Nayak, B.C., Gupta, P.P.,et al, (1983), they found that cardiovascular stability was well maintained and there was no change in blood pressure or heart rate from the basal values after the release of tourniquet irrespective of the concentration or volume of centbucridine used. Cardiac rhythum was normal in all cases. Accidental deflation of cuff after administration of 40 ml. of 0.35% solution of centbucridine in one subject had produced moderate bradycardia. The incidence of other side effects like emesis, restlessness, facial flushing and venous thrombosis was highest in the group where .5% solution of centbucridine was used and lowest in the .25% group. In the experimental studies after intravenous administration of small doses (5-80 microgram/kilogram) of centbucridine they had found a transient rise of 5 to 10% in blood pressure.

Liver has been shown to play an important role in the metabolism of lignocaine (Sung & Truant, (1954), and Geddes, (1958). Peak level of the drug is reached after the release of tourniquet. It may be a factor to be taken into consideration, where bilateral procedures are carried out. The additive effects of previous administration of drug, as shown by Bromage and Robson, (1961), would be considerably magnified when associated with hepatic insufficiency.

Release of metabolites including potassium may be a remote contributing factor for the causation of some of toxic effects associated with the release of tourniquet, (Kennedy, et al, (1965).

The various types of toxic reactions encountered by different workers are depicted here as follows-

Holmes (1963), in the series ofhis 30 cases, 5 patients complained of a sense of drifting away for a few seconds which was relieved spontaneously.

Bell, et al, ; in their series, on 26 cases, found giddiness, detachment, light headedness in 3 patients, and in another 4 cases he noticed cardiovascular disturbance in the form of wandering pacemaker and minor T, wave changes.

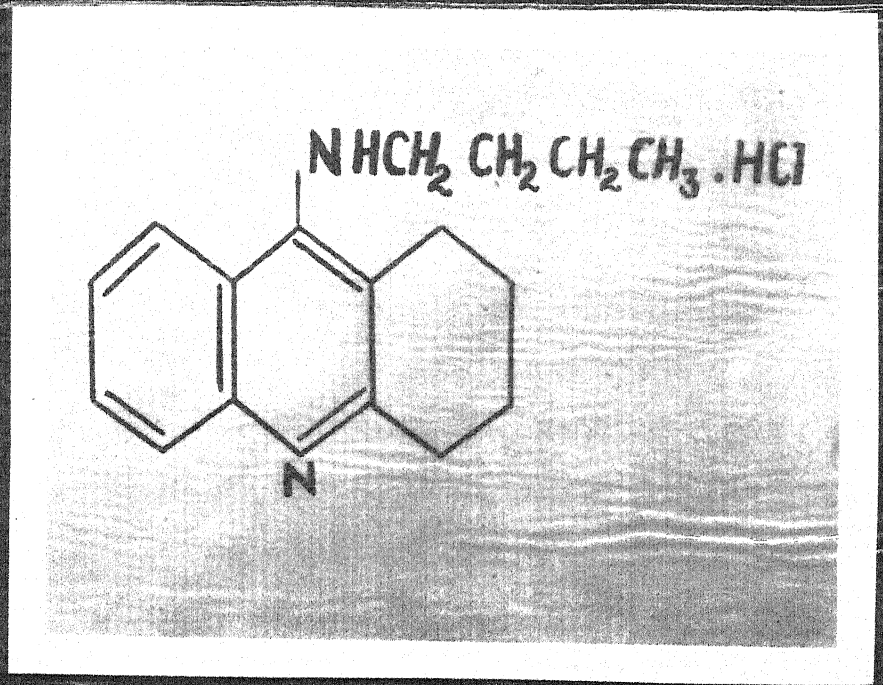
Dawkins, et al.; (1964); found nystagmus, ataxia and some times convulsions in 7 cases in the series of 514 patients.

Cox. J.M.R., (1964), reported twitchings, dizziness and paraesthesia in tongue in 5 out of 47 cases.

Maximum toxic reactions were reported by Kennedy, et al, (1965), drowsiness and unconsiousness in 7 cases, ventricular extra systole in 3 and cardiac arrest in one case.

DRUG:

Centbucridine is a 4-Nbutylamino 1,2,3,4, tetrahydrocridine hydrochloride, 4-N substituted 2,3-poly methylene quinoline (Patnaik, G.K., et al). International non-proprietary name of Centbucridine is BUCRICAINE, given by W.H.O. , Geneva, Switzerland.




Photograph showing chemical structure of centbucridine

Its chemical structure closely resemble, that of the previously existing local analgesic drugs like other local analgesic agents, it also has one hydrophilic amino groupwhich is connected, by an intermediate chain to a lipophilic aromatic radical. Its structure is shown in the photograph.

Changes in any part of the molecule alter the anaesthetic potency and the toxicity of the compound, a fact that provides the basis for the vast number of available local anaesthetics.

Increasing the length of the alcohol group, leads to a greater anaesthetic potency. It also leads to an increase in toxicity so that compounds with an ethyl ester, such as procaine, exhibit the least toxicity. Length of the two terminal groups on the tertiary amino nitrogen is also important.

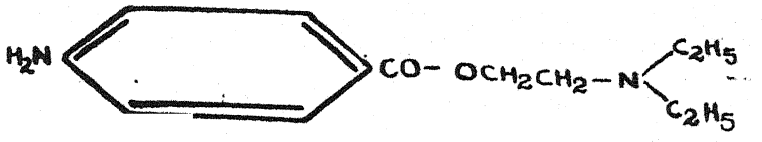
The structure of centbucridine can be compared with the existing local analgesics,(Diagram).

PHARMACOLOGY OF CENTBUCRIDINE:

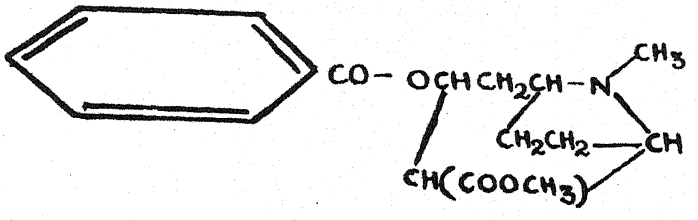
It is a light yellow, crystalline compound of molecular weight 290.9. The melting point of the base is 65 °C and of its hydrochloride, 196 °C. The compound in solid state is stable for about 3½ years on storage at room temperature, while in aquous solution (0.5% concentration) in an atmosphere of nitrogen it is stable for about 1½ years.

LOCAL ANAESTHETIC ACTIVITY:

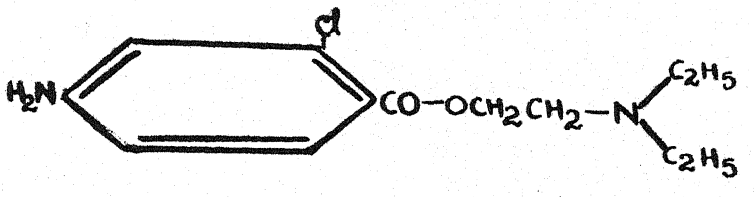
It shows potent and reversible local anaesthetic



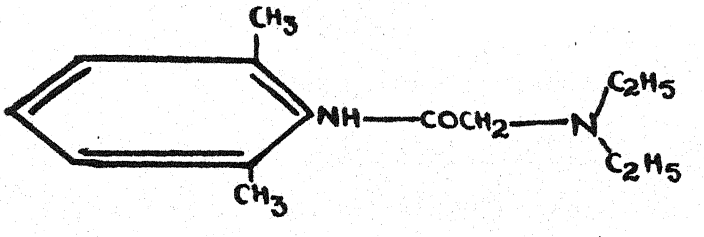

PROCAINE



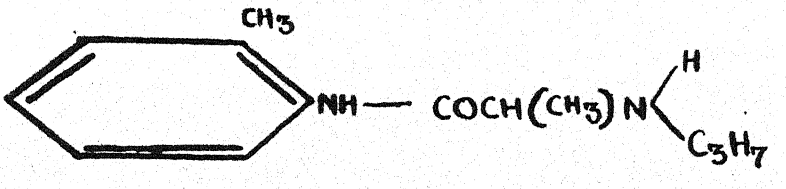

COCAINE



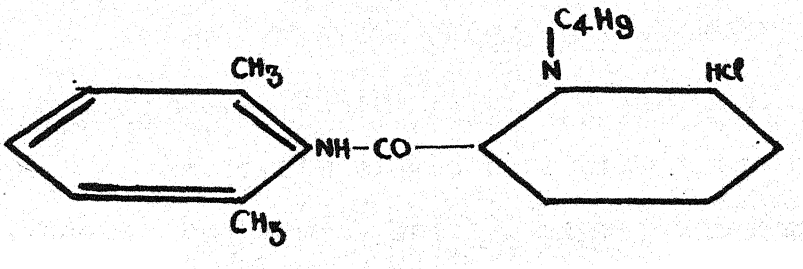

CHLOROPROCAINE




LIDOCAINE




PRILOCAINE




BUPIVACAINE

# STRUCTURAL FORMULAS OF LOCAL ANAESTHETICS

activity. This was evaluated by standard laboratory tests, in the work done at C.D.R.I. Minimum effective concentrations of centbucridine and lignocaine and the duration of effect at these concentrations were determined as follows :-

A. Surface Anaesthesia (Rabbit cornea, Patnaik, G.K., Rastogi, S.N., et al., 1982).

| | Centbucridine | Lignocaine |
|---|---|---|
| Minimum effective concentration | 0.2% | 1.0% |
| Duration in minutes | 15 | 15 |

B. Infiltration Anaesthesia (guinea pig intradermal wheal method).

| | Centbucridine | Lignocaine |
|---|---|---|
| Minimum effective concentration | 0.0125 | 0.1 |
| Duration in minutes | 25 | 20 |

C. Conduction block (blockade of pressor response to central sciatic stimulation in anaesthetised cat by injection of 0.1 cc in the sheath of the nerve proximal to the site of stimulation).

| | | |
|---|---|---|
| Minimum effective concentration | 0.2 | 3.0 |
| Duration in minutes | 100 | 75 |

POTENTIATION OF LOCAL ANAESTHETIC ACTIVITY BY EPINEPHRINE:

As in the case of lignocaine, the local anaesthetic activity of centbucridine is potentiated by epinephrine, but a much smaller amount was required than generally

employed with lignocaine, however, there is a marked increase in the duration of anaesthesia.

| Drug | Concentration | Anaesthesia | Duration |
|---|---|---|---|
| Epinephrine | 5 microgram/cc | - | - |
| Centbucridine | 0.01% | Mild | 7' |
| Centbucridine + 5 microgram/cc epinephrine | 0.01% | Complete | 90' |

EFFECT ON NEUROMUSCULAR TRANSMISSION:

The sciatic nerve anterior tibialis muscle preparation in chloralosed cats was used for this purpose. There was no effect of lignocaine in doses of 10 mg/kg/ I.V. and of centbucridine in doses of 2.5mg/kg I.V. closed intraarterial injection of 400 microgram of centbucridine, however, produced a 100% block, which developed slowly, while lignocaine waswithout any effect upto 1 mg. when administered similarly.

EFFECTS ON C.N.S. :(Patnaik, G.K. and Dhawan, B.N., (1982):

None upto 1/5th $L.D._{50}$. Larger doses produced signs of C.N.S. stimulation like tachypnoea, hyperreflexia, preconvulsions and with toxic doses clonic convulsions preceded by death.

EFFECT ON C.V.S. AND RESPIRATION:

These were studied in cats anaesthetised with chloralose. Centbucridine upto a dose of 2.5 mg/kg I.V. produced a transient, mild, dose dependent hypertension and respiratory stimulation without any effect on nictitating

membrane. The responses to acetylcholine and epinephrine were uneffected but histamine depressor response was completely blocked by 2.5 mg/kg dose. It possesses mild C.N.S. stimulant vasopressor, antihistaminic, spasmolytic and anti-arrhythmic activity.

EFFECT ON ISOLATED GUINEA PIG HEART:

Both centbucridine and lignocaine had a negative inotropic effect. The effect of 20 microgram centbucridine was approximately equivalent to 100 microgram lignocaine.

TOXICITY STUDIES:

Acute toxicity:

This was determined over 24 hrs period using 10 animals at each dose level. The LD50 values in various species are given below :

Mice - 35 mg/kg/i.p. (cf. lignocaine 150 mg/kg/i.p.).

Rats - 45 mg/kg/S.C.

Monkey - 10.5 mg/kg/S.C.

Sub-acute toxicity :

This was evaluated at ½, 1/10, 1/25, 1/50 and 1/100 LD50 in monkeys. No toxic effects were noted in rats and guinea pigs, monkeys in the lower three doses.

Neurotoxicity :

Centbucridine (0.5 and 1%) marcaine (0.5%) and lignocaine (5%) were injected intrathecally twice a week in rabbits for two weeks and no gross or microscopic changes indicative of toxicity, were observed

in the spinal cord or nerves. (Gupta,P.P., Nityanand,S., et al, 1982).

Teratogenecity :

These tests were undertaken in mice (10 and 40 mg/ mice ) and rabbits (4 and 20 mg/rabbit). Centbucridine did not produce any foetal malformation in either species. (Sethi,N. and Mukherjee, S.K., 1982).

# MATERIAL & METHOD

The present study of intravenous regional analgesia with CENTBUCRIDINE was conducted on a number of emergency and planned patients, of A.S.A. group I, operated upon at the M.L.B. Medical College Hospital, Jhansi during the year 1982-83.

The cases, who were to undergo limb surgery, were randomly selected after they were found to be fulfilling the following criteria.

1. Patients should be above 10 years of age to get better co-operation.
2. Duration of surgery should be over 20 minutes.
3. Septic cases were not included so as to avoid the danger of insemination of septic foci after the release of tourniquet.
4. Cases having thromboangitis obliterans were not selected, as, application of the tourniquet would be detrimental to them.
5. Cases with known history of convulsions and hypersensitivity to local analgesic drugs have not been taken.
6. Patients with the history of liver disease were omitted.
7. Patients with invisible veins were avoided.
8. Complicated compound fractures or mutilated crush injuries were excluded from the study, as there

was danger of leakage of the analgesic solution.

9. Patients in shock were omitted.

10. Uncooperative, nervous and patients unwilling for intravenous regional analgesia were also avoided.

PREPARATION OF THE PATIENTS :

The cases under study were first assured and reassured and were also explained about the type and technique of anaesthesia going to be employed in them. They were also made to sign a written consent regarding their acceptance of the technique.

Each patient was then subjected to detail general and systemic examination. Cardiovascular and nervous system were given a thorough check up so as to exclude any possibility of an incipient or apparent pathology.

Pre-operative fasting, if possible was advised for at least 6-8 hours before surgery, in case the technique should fail and general anaesthesia be required. Every case was subjected to sensitivity test 2-3 minims of centbucridine. 01% was injected intradermally on the forearm and the appearence of erythema was watched. Any case where an erythema was noticed the technique was not adopted.

How many S.V.R. cases were detected? where is the observation recorded?

PREMEDICATION :

Usually no premedication was given except, in patients with discomfort or apprehension, where Diazepam 10 mg/or Pentazocine 30 mg were injected intramuscularly.

45-60 minutes before onset of the procedure.

ARMAMENTARIUM :

The apparatus required for the technique is as follows :

1. 0.5 percent centbucridine and distilled water.
2. Large syringe (50 ml is most convenient).
3. Two tourniquets.
4. Gordh's needle 18-20 gauge.
5. Esmarch's bandage.
6. Sterile bowl.
7. Hypodermic needles 20-23 gauge.

DRUG :

The drug used in this technique was a newly synthesized local analgesic, CENTBUCRIDINE. It was used in varying concentrations and depending upon the concentrations of the drug the patients were divided in four groups as per below :

| | | |
|---|---|---|
| Group - | I | .25% |
| Group - | II | .30% |
| Group - | III | .35% |
| Group - | IV | .40% |

How did you prepare these concentrations? How were they stored? How sterilized?

TECHNIQUE :

The whole procedure was carried out under fullaseptic precautions. How were the Solutions Sterilized?

Tourniquets were applied one above the other on the arm or the thigh depending upon the limb involved.

Proximal tourniquet was first inflated followed by inflation of the distal tourniquet and deflation of the former, s imultaneously, after the injection of the drug.

Venepuncture was done by a sterile Gordh needle, as near the site of operation as possible, after applying antiseptic lotions on the skin. The needle was then secured in-situ and flushed with distilled water to avoid blood clotting in it and obstructing the lumen.

Exsanguination was then done by lifting the arm or the leg above heart level so as to drain the extremity of the blood as far as possible. After keeping the limb elevated for five minutes the first tourniquet was inflated 20 mm of Hg above the systolic blood pressure, as mentioned above and time of inflation was noted. The limb was then brought down and the drug was injected. Esmarch's bandage was also used as an alternative method to the gravitational drainage for exsanguination.

The dose of centburcridine depended upon the following factors :

1. The extremity operated upon (upper or lower).
2. Type of operation.
3. Anticipated duration of operative procedure.

After injection of the drug appearance of any toxic reaction or discolouration of the skin was watched. For upper limb surgeries the dose ranged between 100-135 mg while that for lower limb was between 190-240 mg.

The drug available in .5% concentration was suitably diluted by the addition of distilled water to get the desired concentration, depending upon which group the patient belonged.

In case the surgery was prolonged repeat injections were given as and when required. The times of first and subsequent injections, if any, were recorded, as also the duration of effect of the first dose.

Intravenous infusion of 5% Dextrose in D/W was now started for parentral therapy and blood pressure and pulse were monitored every 5-10 minutes after injection of the drug. Surgery was allowed only when the desired effect had been achieved, as assessed by the following schedule regarding the degree of analgesia.

Excellent :

Loss of sensory, touch, pin prick and no pain or discomfort from the operative procedure and there was no tourniquet pain felt by the patient.

Good :

Complete loss of touch and pain sensation. The sensory response to the maximum pressure was retained which if applied to the fingers or the toes nail was interpretted as burning sensation. And there was slight or no tourniquet pain.

Fair :

Incomplete anaesthesia with mild pain or discomfort from the operative procedure and severe or mild tourniquet

pain.

Poor :

Failure of anaesthesia and the surgical procedure was not possible under this technique and general anaesthesia had to be administered.

Patients exhibiting fair and poor responses had to be supplemented with general anaesthesia with nitrous oxide + Oxygen + Halothane or Trichloroethylene. During the course of surgery the pulse and blood pressure were regularly checked along with the continuous E.C.G. monitoring and evidence of any toxic symptoms noted as per following classification :

A. C.N.S. :

i) Stimulant — To the cerebral cortex or medulla.

ii) Depressant — (a) Respiratory system.

(b) Vaso motor system.

B. PERIPHERAL EFFECT :

Cardiovascular — (a) Direct action on the heart.

(b) Action on the vascular bed.

C. ABNORMAL RESPONSE :

(a) Allergy

(b) Hypersensitivity

(c) Idiosyncracy.

After completion of surgery the tourniquet was deflated gradually over a period of five minutes and the time noted. A minimum of 45 minutes were required before

deflation was allowed, no matter how short the surgical procedure. Pulse and blood pressure were checked every 3-4 minutes for the first fifteen minutes and then every fifteen minutes for an hour after surgery. Any evidence of toxic reactions were noted and treated accordingly. Minor toxic reactions like giddiness were usually treated by the administration of oxygen only, for few minutes. The patients were then interrogated as to their acceptability of the technique and its comparision with any anaesthetic experience of the past.

The patients were then transferred to ward and were regularly visited for at least 24 hrs after the procedure. Any sign of subacute toxicity was also looked upon and was given a prompt treatment. Patients who wished were then discharged from the hospital.

# OBSERVATION

## OBSERVATIONS

The present study of 'CENTBUCRIDINE AS INTRA-VENOUS REGIONAL ANALGESIC' has been conducted on a series of 60 patients who were subjected to various surgical procedures and the following observations were drawn:-

TABLE -I

Showing age and sex distribution of the cases.

| Age Group | MALE | | FEMALE | |
|---|---|---|---|---|
| | No of cases | Percentage | No of cases | Percentage |
| 11-20 | 8 | 13.33 | - | - |
| 21-30 | 15 | 25.00 | 2 | 3.33 |
| 31-40 | 13 | 21.66 | 5 | 8.33 |
| 41-50 | 5 | 08.33 | 4 | 6.66 |
| 51-60 | 6 | 10.00 | 1 | 1.66 |
| 61-70 | 1 | 01.66 | - | - |
| Total | 48 | 79.98 | 12 | 19.98 |

1. Patients ranged between the ages of 11-70 yrs.
2. Total no. of 48 (79.98%) males and 12 (19.98%) females were studied. The ratio being 4:1.
3. Maximum number of males, 15(25%), were of the age group of 21-30 yrs, while females 5 (8.33%) were in the age group of 31-40 yrs.

DIAGRAM SHOWING NUMBER OF CASES WITH AGE AND SEX DISTRIBUTION

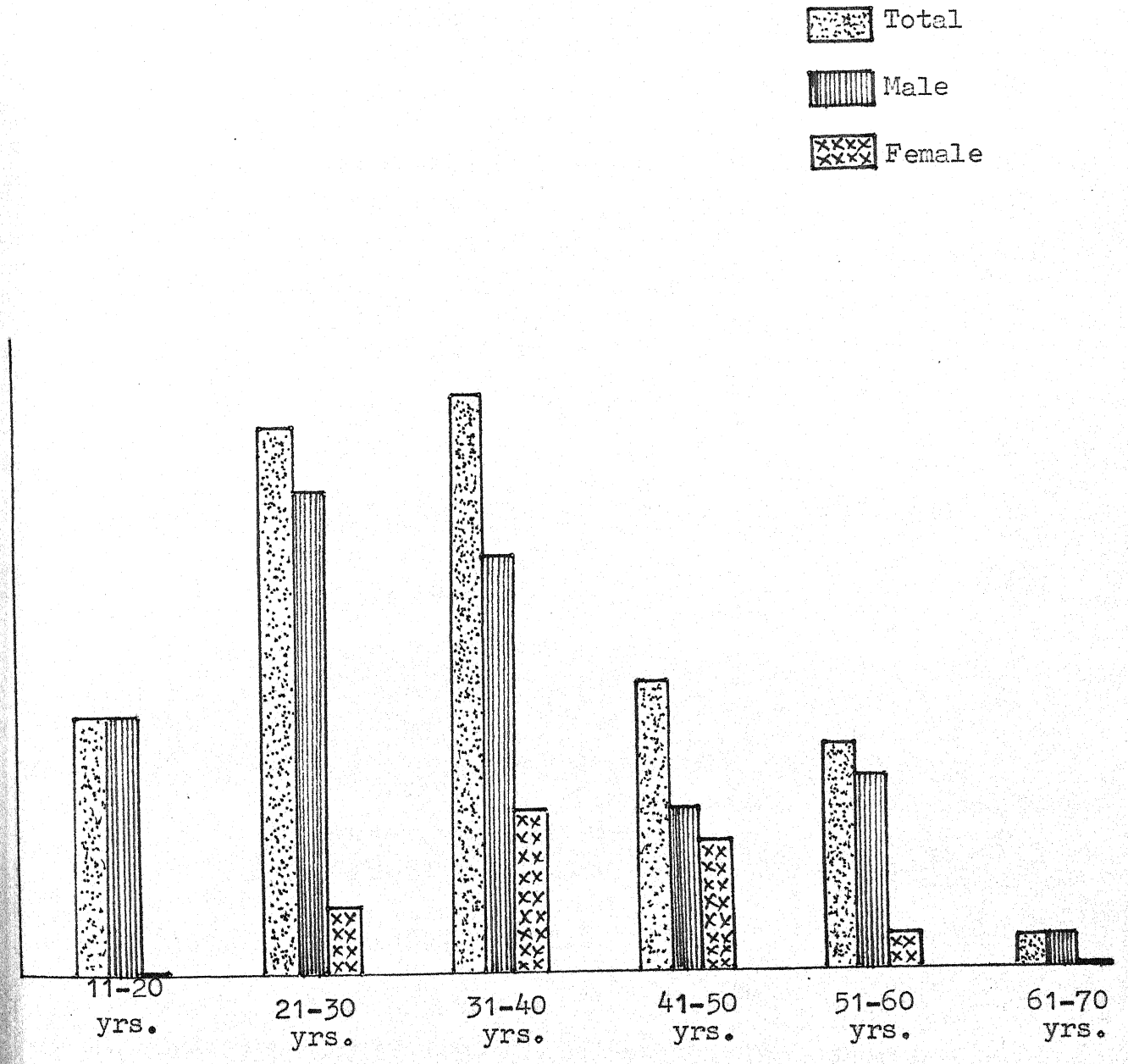


TABLE -II

Showing distribution of cases according to operations performed.

| S.No. | Operation performed | No.of cases | Percentage of Total |
|---|---|---|---|
| A. | UPPER EXTRIMITY | | |
| 1. | Surgical toilet and debridement | 17 | 28.33 |
| 2. | Excision arthro-plasty(Elbow) | 2 | 03.33 |
| 3. | Saucerization | 8 | 13.33 |
| 4. | Arthrodesis of M.P. Joint. | 2 | 03.33 |
| 5. | Reconstruction of fingers(Syndactyly) | 2 | 03.33 |
| 6. | Correction of finger deformity | 5 | 08.33 |
| B | LOWER EXTREMITY | | |
| 1. | Surgical toilet and debridement | 10 | 16.66 |
| 2. | Excision of Head of 5th metatarsal | 4 | 06.66 |
| 3. | Excision of si nus | 2 | 03.33 |
| 4. | Charnley's compression arthrodesis | 2 | 03.33 |
| 5. | Synovectomy (Knee) | 3 | 05.00 |
| 6. | Sims amputation | 2 | 03.33 |
| 7. | Excision of epider-moid Carcinoma | 1 | 01.66 |
| | Total | 60 | 100 |

TABLE-III

Showing distribution of patients according to the concentration of the drug used.

| Group | Concentration of drug | Number of cases | Percentage |
|---|---|---|---|
| I | .25 | 15 | 25 |
| II | .30 | 15 | 25 |
| III | .35 | 15 | 25 |
| IV | .40 | 15 | 25 |
| | | 60 | 100% |

Depending upon the concentration of the drug used the patients were divided into 4 groups of 15 patients each.

TABLE-IV

Showing total dose injected in various groups.

| Group | | Total dose in ml.(mg.) | | | |
|---|---|---|---|---|---|
| | | Upper limb | (mg.) | Lower limb | (mg.) |
| I | Mean | 42.14 | (105.35) | 76.25 | (190.62) |
| | S.D. | ±2.67 | (± 6.68) | ±3.53 | (± 8.83) |
| II | Mean | 38.75 | (116.25) | 68.57 | (205.71) |
| | S.D. | ±2.31 | (± 6.93) | ±2.43 | (± 7.29) |
| III | Mean | 34.37 | (120.29) | 63.57 | (222.49) |
| | S.D. | ±3.20 | (±11.2) | ±2.43 | (± 8.50) |
| IV | Mean | 30.62 | (122.48) | 56.42 | (225.68) |
| | S.D. | ±3.20 | (±12.8) | ±3.77 | (±15.08) |

1. Total dose depended upon the concentration of the drug.
2. It was maximum when concentration was .25% i.e. 42.14 ml ± 2.67 ml for upper limb and 76.25 ml ± 3.53 ml for lower limb.
3. Minimum volume injected was with .4% concentration i.e. 30.62 ml ± 3.20 and 56.42 ml, ± 3.77 ml for upper and lower limbs respectively.

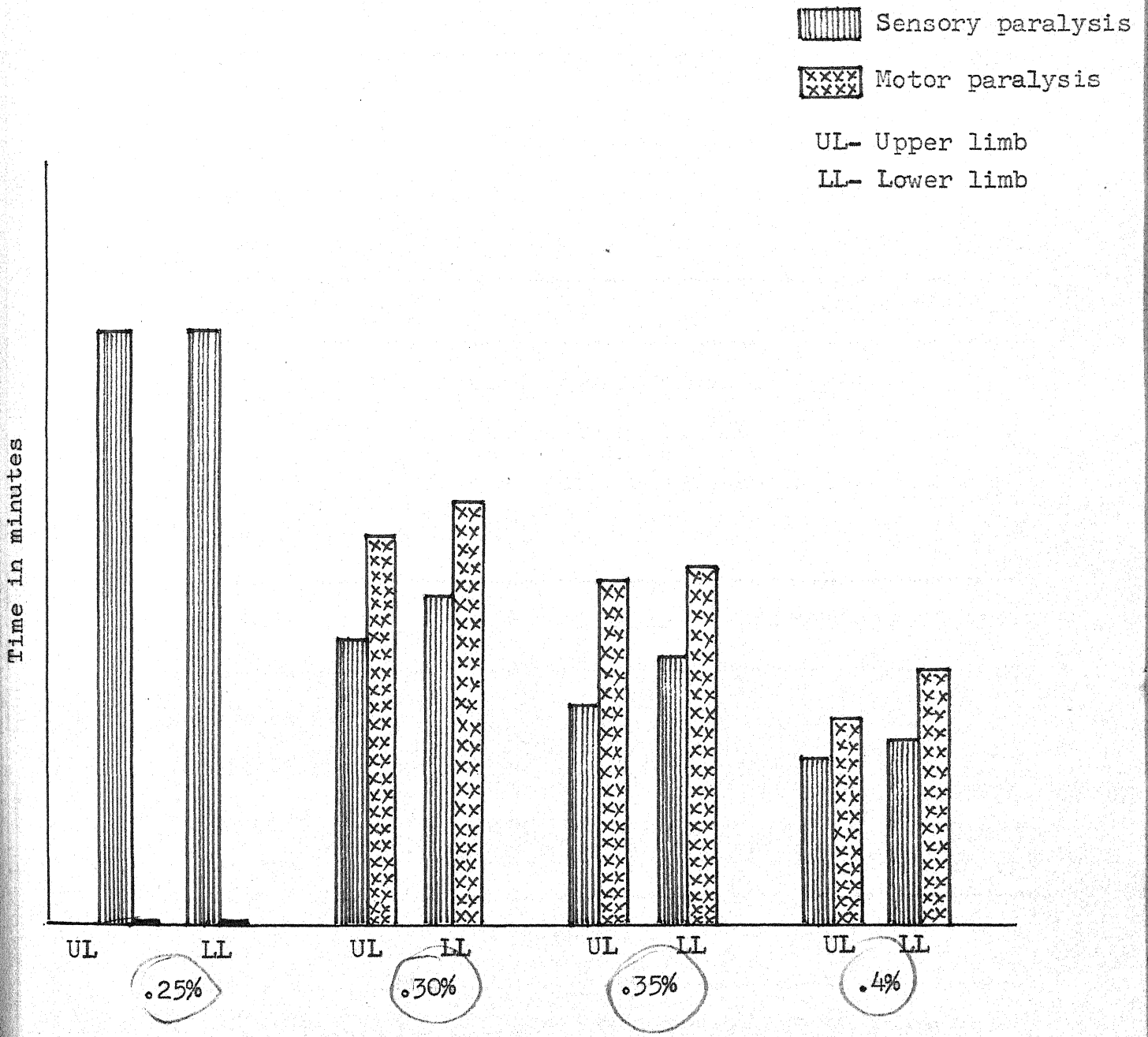
TABLE-V

Showing average time of onset of analgesia in different groups.

| Group | | Total time in minutes | | | |
|---|---|---|---|---|---|
| | | Upper limb | | Lower limb | |
| | | Sensory | Motor | Sensory | Motor |
| I | Mean | 5.00 | - | 5.00 | - |
| | S.D. | ± 1.15 | - | ± 1.06 | - |
| II | Mean | 2.37 | 3.25 | 2.71 | 3.57 |
| | S.D. | ± .91 | ± 1.03 | ± .48 | ± .97 |
| III | Mean | 1.87 | 2.87 | 2.28 | 3.00 |
| | S.D. | ± .83 | ± .83 | ± .95 | ± .81 |
| IV | Mean | 1.37 | 1.75 | 1.57 | 2.14 |
| | S.D. | ± .51 | ± .70 | ± .53 | ± .69 |

1. The duration of onset of analgesia is inversely proportional to the concentration of the drug.
2. Motor paralysis in both upper and lower limbs was not seen with .25% concentration of the drug.
3. Maximum time (5.00 minutes) was taken for analgesia to be complete with .25% concentration and minimum

DIAGRAM SHOWING TIME TAKEN FOR SENSORY AND MOTOR PARALYSIS OF THE UPPER AND LOWER LIMBS AFTER ADMINISTRATION OF CENTBUCRIDINE IN VARIOUS GROUPS.



(1.75 minutes) with .4% concentration.

TABLE-VI

Showing Analgesic Effect in various Groups

a-Group-I

| Effect | No. of cases | Percentage of cases |
|---|---|---|
| Excellent | - | - |
| Good | 4 | 26.66 |
| Moderate | 7 | 46.66 |
| Poor | 4 | 26.66 |
| Total | 15 | 100.00 |

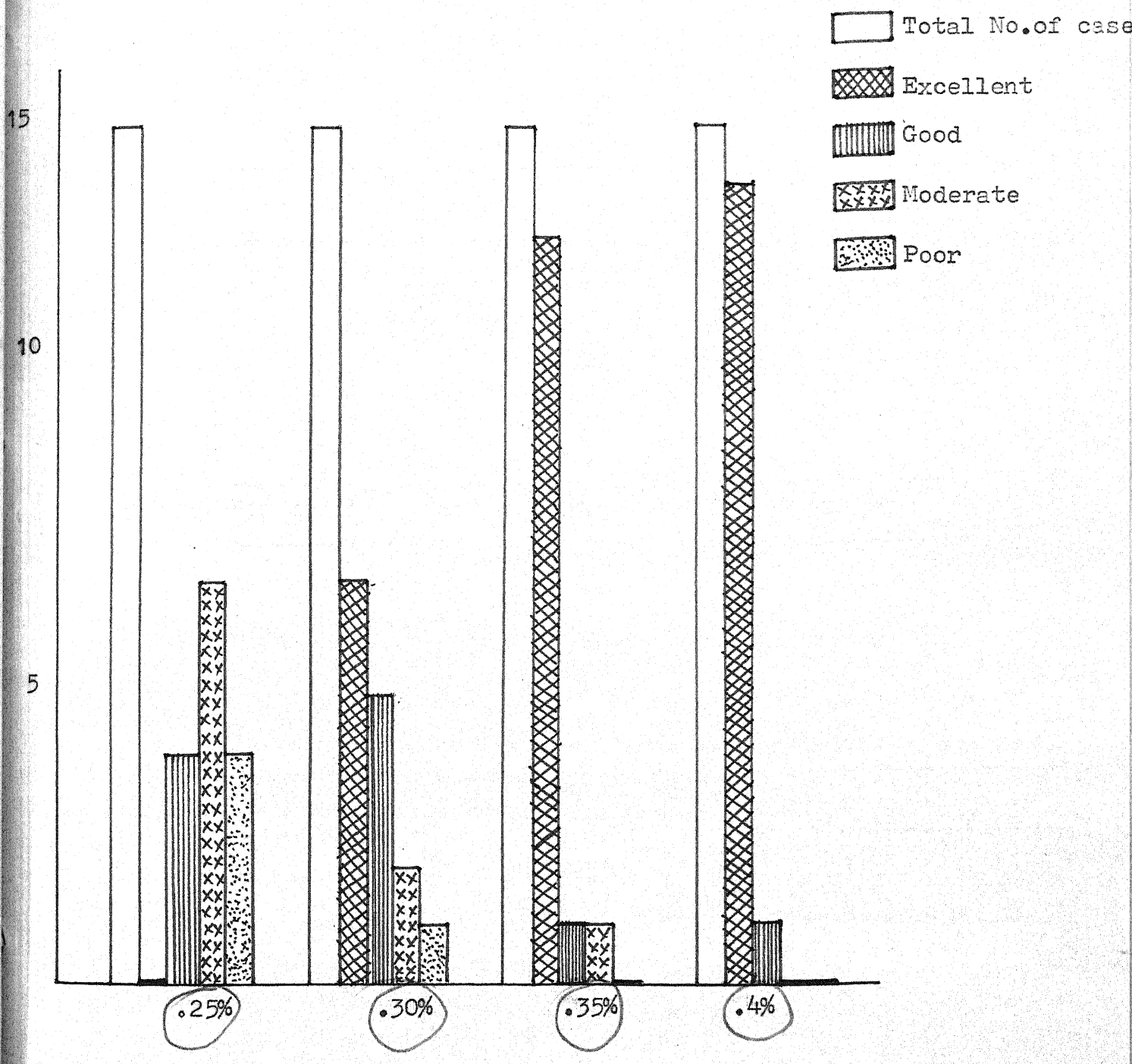
1. None of the cases showed excellent result.
2. Good result was observed in only 26.66% of cases.
3. Failure of anaesthesia was there in 26.66% cases.

b-Group-II

| Effect | No. of cases | Percentage of cases |
|---|---|---|
| Excellent | 7 | 46.66 |
| Good | 5 | 33.33 |
| Moderate | 2 | 13.33 |
| Poor | 1 | 06.66 |
| Total | 15 | 100.00 |

Excellent results were observed in 46.66% cases where as in 6.66% cases there was failure of anaesthesia.

DIAGRAM SHOWING DEGREE OF ANALGESIA IN VARIOUS GROUPS



c-Group-III

| Effect | No. of cases | Percentage of cases |
|---|---|---|
| Excellent | 13 | 86.66 |
| Good | 1 | 6.66 |
| Moderate | 1 | 6.66 |
| Poor | - | - |
| Total | 15 | 100.00 |

1. Excellent result is seen in 86.66% cases, good/ moderate result in 6.66% each.
2. Failure is not observed in this group.

d-Group-IV

| Effect | No. of cases | Percentage of cases |
|---|---|---|
| Excellent | 14 | 93.33 |
| Good | 1 | 6.66 |
| Moderate | - | - |
| Poor | - | - |
| Total | 15 | 100.00 |

1. 93.33% cases exhibited excellent result.
2. None of the patients failed to develop analgesia.

TABLE-VII

Showing duration of action of the drug and tourniquet time in various groups.

| Group | Duration in minutes | | | |
|---|---|---|---|---|
| | Duration of action | | Tourniquet time | |
| | Mean | S.D. | Mean | S.D. |
| I | 31.00 | ±8.70 | 53.06 | ±3.41 |
| II | 68.26 | ±7.25 | 74.86 | ±2.92 |
| III | 83.4 | ±6.03 | 83.4 | ±6.03 |
| IV | 86.6 | ±3.85 | 86.6 | ±3.85 |

1. In groups I & II effect of the drug had gone before the deflation of the tourniquet cuff.
2. There was no waning of analgesic effect throughout the procedure in groups III & IV.

TABLE-VIII

Showing time taken for the reestablishment of sensations, in various groups after the release of tourniquet.

| Group | Time taken for the return of sensations after the release of tourniquet(in minutes) | |
|---|---|---|
| | Mean | S.D. |
| I | - | - |
| II | - | - |
| III | 17.26 | ±1.57 |
| IV | 27.13 | ±1.80 |

1. Sensations had already returned in groups I & II before the deflation of the tourniquet.
2. Maximum time of 27.13 minutes ( ± 1.80 ) was taken for the sensation to return in group.IV.
3. Time taken for the re-establishment of sensation is directly proportional to the concentration of the drug used in that group.

a-Group-I

## TABLE-IX

Showing cardiovascular and respiratory changes in each group:-

| Period | Pulse/minute | | Blood Pressure (in m.m. of Hg) | | | | Respiration (Rate per minute) | | E.C.G. Monitoring |
|---|---|---|---|---|---|---|---|---|---|
| | | | Systolic | | Diastolic | | | | |
| | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | |
| Pre operative | 80.53 | ±7.83 | 124.8 | ±22.37 | 74.8 | ±10.16 | 16.26 | ±1.98 | Normal |
| Per operative | 80.8 | ±8.20 | 125.73 | ±22.12 | 74.93 | ±10.13 | 16.86 | ±1.76 | Normal |
| Post operative | 79.73 | ±8.20 | 126.0 | ±22.52 | 75.6 | ± 9.83 | 17.46 | ±1.88 | Normal |
| t-value | | .273 | | .146 | | .219 | | 1.71 | |
| p-value | | ∠0.10 | | ∠0.10 | | ∠0.10 | | ∠0. 05 | |

1. Pulse showed bradycardia of 1-2 beats per minute in the post operative period.
2. Both systolic and diastolic blood pressure showed slight rise from the preoperative level.
3. Respiration shows rise of 1-2 breaths per minute.
4. No arrhythmia was observed and E.C.G. was normal throughout the procedure.

b-Group-II

| Period | Pulse/minute | | Blood Pressure (in m.m. of Hg) Systolic | | Blood Pressure (in m.m. of Hg) Diastolic | | Respiration (Rate per minute) | | E.C.G. Monitoring |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | |
| Pre operative | 80.26 | ±9.37 | 126.8 | ±20.25 | 76.0 | ±8.14 | 15.8 | ±1.61 | Normal |
| Per Operative | 79.86 | ±9.11 | 128.26 | ±19.79 | 77.2 | ±8.02 | 16.66 | ±1.63 | Normal |
| Post operative | 79.06 | ±9.58 | 129.73 | ±19.91 | 78.66 | ±7.35 | 17.86 | ±1.59 | Normal |
| t-value | | .347 | | .40 | | .94 | | 3.527 | |
| p-value | | ∠0.10 | | ∠0.10 | | ∠0.10 | | ∠0.001 | |

1. Pulse shows a bradycardia of 1-2 beats per minute in the post operative period.
2. Both systolic and diastolic blood pressure were higher from the basal level in the post operative period.
3. Respiration was increased by 2 breaths per minute in the post operative period.
4. E.C.G. was normal.

c-Group-III

| Period | Pulse/minute | | Blood Pressure (in m.m. of Hg) | | | | Respiration (Rate per minute) | | E.C.G. Monitoring |
|---|---|---|---|---|---|---|---|---|---|
| | | | Systolic | | Diastolic | | | | |
| | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | |
| Pre operative | 81.86 | ±8.05 | 125.6 | ±21.6 | 74.8 | ±10.16 | 16.26 | ±2.18 | Normal |
| Per operative | 80.93 | ±7.88 | 126.8 | ±21.36 | 75.86 | ±9 .72 | 17.4 | ±2.02 | Normal |
| Post operative | 79.86 | ±7.61 | 130.53 | ±20.81 | 76.53 | ±9. 75 | 19.0 | ±1.46 | Normal |
| t-value | .70 | | .637 | | .471 | | 4.126 | | |
| p-value | ∠0.10 | | ∠0.10 | | ∠0.10 | | ∠0.001 | | |

1. Pulse shows a bradycardia of 1-2 beats per minute.
2. Systolic and diastolic blood pressures are raised in the post operative period.
3. Respiratory rate is increased by 2-3 breaths per minute.
4. E.C.G. is normal throughout the procedure.

d-Group-IV

| Period | Pulse/minute | | Blood Pressure (in m.m. of Hg) | | | | Respiration (Rate per minute) | | E.C.G. Monitoring |
|---|---|---|---|---|---|---|---|---|---|
| | | | Systolic | | Diastolic | | | | |
| | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | |
| Pre operative | 82.66 | ±7.31 | 125.46 | ±18.92 | 77.33 | ±7.88 | 16.33 | ±1.87 | Normal |
| Per operative | 81.06 | ±7.47 | 128.0 | ±19.24 | 81.06 | ±7.77 | 18.4 | ±1.95 | Normal |
| Post operative | 80.0 | ±7.44 | 132.4 | ±19.42 | 83.46 | ±6.90 | 20.0 | ±1.00 | Normal |
| t-value | | .988 | | .992 | | 2.27 | | 7.01 | |
| p-value | | $\angle$ 0.10 | | $\angle$ 0.10 | | $\angle$ 0.10 | | $\angle$ 0.001 | |

1. Pulse shows bradycardia of 2-3 beats per minute.
2. Steady rise in systolic and diastolic blood pressure is seen in proportion to the concentration of the drug.
3. Respiration shows a significant rise of3-4 breaths per minute in thepost operative period.
4. E.C.G. is normal in all the phases of the procedure.

TABLE-X

Showing incidence of supplementation required in various groups.

| Group | Diazepam (10mg) | | Pentazocine (30mg) | | Diazepam + Pentazocine | | $N_2O + O_2$ | | $N_2O + O_2$ + Trilene/Halothane | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No.of cases | % | No.of cases | % | No.of cases | % | No.of cases | % | No.of cases | % |
| I | - | - | - | - | 3 | 20 | 3 | 20 | 2 | 13.33 |
| II | - | - | - | - | 1 | 6.66 | 1 | 6.66 | - | - |
| III | - | - | 1 | 6.66 | - | - | - | - | - | - |
| IV | 1 | 6.66 | - | - | - | - | - | - | - | - |

1. Maximum supplementation were required in the group I.

2. In groups III and IV equal number of (6.66%) cases required sedation only.

TABLE-XI

Showing incidence ofimmediate and delayed complications.

| Toxic effect | Group I | | Group II | | Group III | | Group IV | |
|---|---|---|---|---|---|---|---|---|
| | No. of cases | % | No. of cases | % | No. of cases | % | No. of cases | % |
| A. IMMEDIATE | | | | | | | | |
| Nausea & Vomiting | - | - | 3 | 20 | 4 | 26.66 | 6 | 40 |
| Restlessness | 1 | 6.66 | 1 | 6.66 | 2 | 13.33 | 3 | 20 |
| Facial flushing | - | - | - | - | 1 | 6.66 | 2 | 13.33 |
| Drowsiness | - | - | - | - | - | - | 1 | 6.66 |
| B. DELAYED | | | | | | | | |
| Venous thrombosis | - | - | - | - | - | - | 1 | 6.66 |
| Gangrene | - | - | - | - | - | - | 1 | 6.66 |

1. Incidence of toxicity is directly proportional to the concentration of the drug.
2. Maximum number of different toxicities were seen in group IV.
3. Lowest and insignificant toxicity is seen in group I.

TABLE-XII

Showing opinion of the patient for this technique.

| S.NO. | Preference | No. of cases | Percentage |
|---|---|---|---|
| 1. | General anaesthesia | 9 | 15 |
| 2. | Intravenous regional analgesia | 46 | 76.66 |
| 3. | No preference | 5 | 8.33 |
| | Total | 60 | 100 |

Each patient was asked whether he would prefer general anaesthesia to intravenous regional analgesia if he was to have the same operation again. 76.66% patients liked the technique.

15% cases preferred general anaesthesia to intravenous regional analgesia, due to the poor results with lower concentration in their case. 8.33% patients had no particular choice, any of the technique was equally good for them.

# DISCUSSION

## DISCUSSION

Intravenous administration of a local analgesic drug, to provide pain relief during surgery, on the limb, although theoretically, a good and sure technique as compared to the cumbersome and unpredicatable regional blocks, yet, has not very much enjoyed the acceptance of modern anaesthesiologists, largely because of the toxicity reactions of the drugs in use. Most of these drugs have the principal disadvantage of being central nervous and cardiovascular system depressants and these two singled out mar their efficacy as intravenous regional analgesics.

A drug devoid of such toxicity reactions would definitely prove a boon to the simple and effective technique, particularly for an anaesthetist working under field conditions.

Centbucridine, a polymethylene quinoline derivative, which shows potent and reversible local anaesthetic activity in animals and man, both by infiltration and topical application (Patnaik, G.K., et al, 1982), as well as by the intravenous administration (Suri, et al, 1983), claims an upper hand over its other counterparts firstly, because of its central nervous system stimulant action and secondly, due to its cardiovascular stabilising property. It therefore merits a trial as an agent for intravenous regional analgesia.

The present study, on 60 adult patients, was done

to establish the efficacy of centbucridine as an intravenous regional analgesic. This being an almost original work, is devoid of much literature to support our results, except that of Suri, et al, (1983), who maintain the drug to be very potent and effective, more than the conventional lignocaine et al.

The subjects for this study were 48 males and 12 females ranging between 11-70 yrs. of age, undergoing both planned (33) and emergency (27) operations (Tables I & II). Children were excluded from the study as they are less co-operative and donot appreciate the idea of a needle being plunged into their arms or feet. Most of the other workers have also excluded children below the age of 10 yrs. for the same reason. (Sorbie & Chacha, 1965, Holmes, C.McK, 1963, Mittal, N.K., et al, 1972).

The site of operation in this technique could only be upto the lower one third of the arm or thigh, as the presence of a continuous and uninterrupted tourniquet is a must, which would therefore hinder with the surgical procedures if applied for surgeries on arm or thigh.

Premedication of any sort was avoided in all but few (2) emergency cases, where because of the lesion the patients had pain, rendering them restlessand uncooperative, Assurance, reassurance and explanation of the technique proved sufficient for the patients to accept the procedure. Premedication was avoided for the fact that

it would, firstly mask the effect of drug thereby giving false results and secondly it would delay the stay of patients in the hospital. There has been a general agreement, about the avoidance of premedication, by most workers who have opined that sedative premedication would be detrimental to the rapid recovery from the effects of anaesthesia (Sadove, et al, 1952 , and COX, JMR 1964).

As far as sensitivity to the drug is concerned, Centbucridine, after extensive laboratory and clinical trials, has not been found to produce any hypersensitivity reaction, on the contrary it has been shown to carry antihistaminic property, by way of its antagonism of the depressor response to histamine as also blockade of the $H_1$ histamine receptor in the cardiovascular system and guinea pig ileum (Patnaik, G.K. and Dhawan, B.N., 1982). Sensitivity to local analgesic drugs, in general, is also not very common and to quote Moore and Bridenbaugh (1962), " In less than 2% of cases in whom systemic symptoms arise after the administration of a local analgesic, can a true allergy to the drug be imputed."

The use of single tourniquet in the past always had the disadvantage of tourniquet discomfort and pain during the procedure and has therefore discredited its popularity until, Morrison,in 1931, advocated the use of double cuff tourniquet, which was adopted in clinical practice by Bell, et al, (1963), and Adams, et al, (1964), whereby they reported minimum such discomfort. With the

same aim it was decidedto use double cuff tourniquet in our series in all cases, with quite encouraging results.

To achieve uniform and complete spread of the drug the veins were perforated in the distal part of the extremity (dorsum of the hand/foot), as proximal injection would giveincomplete effect, because of the powerful venous valves obstructing downward flow of the drug (Sorbie and Chacha, 1965). One of the cases however required venesection because of the inaccessible veins, which again was performed as distal as possible.

Colbern, E.C., (1970), discouraged the use of Esmarch's bandage, which was till then the most popular method of exsanguination and reasoned that gravitational method is equally as effective and avoids the problem of needle dislodgement and pain during application of the bandage, Same prindiple adopted in our series showed that gravitational drainage inno way hampers the spread of the drug and uniformity of analgesia. On the other hand it produced satisfactorily dry operative field with minimum blood loss.

Dose and concentration of the drug:-

Depending upon the concentration of the drug the patients were divided into four groups of 15 each (Table III). The concentrations used were .25,.3,.35 and .4%. In contrast Suri, et al, (1983), used .25, .35 and .5% concentration. Onthe other hand most of the other drugs

were used in comparatively higher concentrations to get an equal response. Sorbie & Chacha (1965) and majority of other workers have used lignocaine in .5% concentration while Dawkins, et al, (1964), used it in 1% concentration.

Prilocaine has mostly been used in .5% concentration (Kerr,J.H. 1967), and Dunbar & Mazze, 1967), but concentration as high as 2% have also been administered (Hooper, R.L., 1964).

Chloroprocaine in a concentration of 2% has been recommended (Dickler, et al, 1965). Only bupivacaine has been used in low concentration i.e. .25% (Moore, DC and Bridenbaugh, L.D., 1971).

Differing concentrations used in our series, were to establish an optimal concentration of centbucridine which could give adequate analgesia with minimum or no toxic effects, when administered through the vein.

On an average the volume required in each case ranged between 30-45 ml. for the upper extremity and 56-77 ml. for the lower extremity (Table IV). Suri, et al, while working on the upper limb alone have recommended average volume of 35 ml. for the extremity. The volume used were inversely proportional to the concentration of the drug and was so arranged that the dose in mg remained almost the same in every case i.e. between 100-135 mg. for the upper extremity and

190-240 mg for the lower extremity. In contrast the doses required with other local analgesics are comparatively very high (Lignocaine 200-400 mg. , Chloroprocaine upto 800 mg. , Prilocaine 200-800 mg. ), with the exception of bupivacaine which is recommended in almost similar quantity i.e. 75-150 mg.

Time of onset of Analgesia :

Lower the concentration of the drug more was the time required for the onset of its action. In group I the patients required almost 5 minutes for the onset of action while in group IV sensory loss was observed in 1-2 minutes only while motor loss was seen in 2-3 minutes (Table V). In striking contradiction to our findings Suri, et al, (1983), observed almost equal time of onset of analgesia in all groups and have found that it required about 5 minutes ± for the sensory loss and 6 minutes ± for the motor loss.

The time of onset for other local analgesics as observed by other workers shows that minimum time is taken by lignocaine i.e. 3-5 minutes (Atkinson, et al, (1965), and maximum time of 11 minutes is taken by bupivacaine (Moore & Bridenbaugh, et al, 1971). Centbucridine so far takes minimum time for the production of adequate analgesia.

Effect of Analgesia:

The drug is found to produce substantially good

analgesia when used in concentration, more than .3%. As shown in tables VI-a to -d, it can be found that the degree of analgesia was excellent/good in 93% and 100% cases with .35 and .4% concentrations respectively.

On the other hand it was 26.66% with .25% concentration and about 80% with .3% concentration. Both these later groups exhibited rather unsatisfactory quality, in 73% and 20% cases respectively. It can therefore be inferred that concentrationabove .3% are better suited for surgical manoeuvers.

Suri, et al (1983), in agreement to our findings also discard .25% concentration and suggest .35% as the minimum required concentration for the effective analgesia. The effect of analgesia with lignocaine has ranged between 70-96% with minimum advisable concentration (Holmes, C. Mck 70%) Sorbie and Chacha 85%, Schiller, M.G. 91% and Dunbar, et al, 96% ), Dawkins using concentration as higher as 1% lignocaine could get only 95% good results while on the other hand a concentration as low as .4% in our series exhibited 100% response.

Injection tourniquet release time interval:

In none of the cases, tourniquet was released earlier than 45 minutes, no matter howsoever short the operative procedure had been.

Bier, (1908), stated that toxic reactions appear to be more common when the injection release time interval is less than 25 minutes. Morrison (1931), recommended

the time interval to be 30 minutes. Dawkins, et al, (1964), in their series had the time interval as low as 10 minutes, but the quantity and concentration of the drug also had been higher, hence it becomes difficult to explain which of the two factors are to be blamed for the incidence of toxic reactions in their series, as according to Tucker & Boas, 1971, " Peak levels after cuff release were inversely proportional to the tourniquet application time, they also tended to be lower (by about 40%) when the same dose was given in .5% instead of 1% solution."

The tourniquet was not deflated in a single jerk but it was cycled as suggested by Colbern, E. C., (1970), deflating the cuff for 5 seconds and then reinflating for 45 seconds and the cycle was repeated 5-6 times before finally removing the tourniquet.

In every cases tourniquet was kept in place till the end of surgery and was then deflated. This was done to be sure that effect does not diminish with the release of tourniquet.

Duration of Analgesia:

One of the most striking features of the technique is that the duration of analgesia lasts as long as the tourniquet cuff remains inflated, provided of course, the drug effect has set in , as observed by Holmes, C.Mck., 1963, Hooper, R.L., 1965, Dickler, et al, (1965), and Moore and Bridenbaugh, 1971.

In agreement to the above findings table VII shows that duration of analgesia in groups III and IV was complete and uniform throughout the inflation time, thereby it started diminishing. Average duration in these two groups was 83.4 minutes and 86.6 minutes respectively. On the other hand group I and II with their respective duration of 31 minutes and 68.26 minutes, showed diminuation of analgesia even before the deflation of tourniquet as evidenced by the prolonged inflation time and supplementation of general anaesthesia in these cases.

Suri, et al, (1983) with a short inflation period of 20 minutes, evidenced a very long duration of analgesia in volunteers receiving. 35% concentration solution. They achieved good sensory and motor loss for about 3-6 hrs. They however agree with us that .25% solution had almost equal duration of action 37 minutes. In striking contradiction to their findings the cases in our series showed that effect started diminishing in 5-10 minutes in groups III & IV with the complete return of sensation within 17 and 27 minutes respectively, after deflation of the tourniquet.

Holmes, (1963), found that it took 5-10 minutes for the return of sensation after lignocaine, and similarly 10-15 minutes after chloroprocaine(Dickler, et al, 1965), Hooper, however showed a varying period of 1-90 minutes for re-establishment of sensation after intravenous regional prilocaine.

The longest post-deflation analgesia observed so far was with bupivacaine which took on an average 163 minutes for the return of complete sensation, with the effect starting to diminish at 27th minute of release of tourniquet.

This early diminuation of effect could well be explained that with the re-establishment of circulation the drug is washed off from the still disputed site of its action. (Sorbie and Chacha, 1965), proving therefore that the drug acts most probably at the nerve terminals instead of the nerve trunks (Fleming, et al, 1966).

The supplimentation of anaesthesia with $N_2O + O_2$ + trilene/halothane or $N_2O + O_2$ or with Pentazocine (30mg)+ Diazepam (10 mg) was required in maximum number of cases 53.3% in group I. In groups III and IV only 6.6% cases, for each, required supplementation in the form of either pentazocine (30 mg) or Diazepam (10 mg) to alleviate tourniquet discomfort in the later part of the procedure (Table X).

CARDIOVASCULAR AND RESPIRATORY CHANGES:

Kennedy, et al, (1965), using lignocaine observed a fall, by 10 beats per minute in the pulse rate in 15% of their cases, after the release of tourniquet. The blood pressure also showed hypotensive trend with no effect on the respiration. Prilocaine however produced a stable cardiovascular and respiratory systems (Hooper, R.L. 1965). Bupivacaine on the contrary produced hypotension

as observed by Moore and Bridenbaugh, (1971).

Centbucridine has been found to produce a near perfect cardiovascular stability both during and after the technique, A concentration dependant marginal fall in pulse rate and insignificant rise in blood pressure were features to be noted (Table IX a-d). The changes were more evidenced after the release of tourniquet. Continuous E.C.G. monitoring, throughout the procedure and even in the post operative period, showed no evidence of any abnormality in the cardiac function, proving therefore, that the drug, with remarkable cardiovascular stability, has a merited use in poor risk patients.

The rise in blood pressure however can be attributed to vasopressor and antihistaminic property of the drug coupled with the feeling of pain as a result of an early return of sensations. Suri et al, (1983), also prove, on experimental and human trials that the drug no doubt produces a near perfect stability of the heart and general circulation.

The respiratory system however showed a significant rise in the rate by 1-4 breaths per minute, which was directly proportional to the concentration of the drug used. The depth of respiration remained adequate with no evidence of insufficiency. The central nervous system stimulant action of the drug along with peripheral stimuli arising from the site of operation can well be attributed to this response.

Incidence of toxicity:

A wide variety of toxic reactions have been described with the drugs, so far conventionally used, in this technique. Kennedy, et al, (1965), using lignocaine found vertigo, complete loss of consiousness, atrial and ventricular extrasystole and sinus bradycardia etc. Harris, et al, found light headedness, sense of detachment and muscular twitchings. Dunbar, et al, in addition to some of the above mentioned toxicity reactions observed convulsions and blurred vision. Cox. J.M.R., noticed tinnitus and paraesthesia in tongue.

Chloroprocaine is associated with the production of thrombophlebitis (Harris, et al, 1965, Dickler, D.J., 1965, and Harris, W.H., 1969).

Prilocaine is responsible for the production of methaemoglobinaemia in significant number of cases (Harris, et al, 1965, Daly, et al, 1969, Dunbar and Mazze, (1967).

On the contrary centbucridine has been found to produce only minor toxicity reactions like nausea and vomiting, restlessness, facial flushing, drowsiness and venous thrombosis (Table 11). This again was found to be concentration dependent, showingthe maximum incidence in group IV and minimum in group I. In group I only one patient (6.66%) was observed to be restless after the release of tourniquet, which was controlled by injection diazepam (10mg) and $O_2$ in halation. Ingroup III, 7 out

of 15 cases showed minor reactions in the form of nausea and vomitting (4 cases, 26.66%), restlessness (2 cases, 13.33%) and facial flushing (1 case, 6.66%). Maximum incidence of toxicity was observed in group IV where almost 93.33% of the cases showed incidence of minor/major toxicity. Major toxicity was observed only in group IV in the form of venous thrombosis (one case ) and gangrene of the lower extremity (one case ). The cause of gangrene well could be, prolonged intense vasoconstriction as a result of high concentration of the drug in a patient who was grossly anaemic and hypertensive. The limb which was already exposed to anaemic hypoxia and high blood flow rates as a result of hypertension, naturally does not withstand tourniquet for such long a time as 105 minutes in this case. This tourniquet time in itself, which was already more than the recommended time of 90 minutes for a normal limb, can lead to gangrene in an already predisposed limb.

Suri, et al, (1983), observed minor toxicity reactions with .35% and .5% concentration of the drug in the form of emesis, restlessness, facial flushing, drowsiness and localised burning sensations and among major toxicity reactions they found that drug produced venous thrombosis in 2 cases where .5% concentration was used.

When asked, on the completion of the procedure,

about the preference of the technique, as compared to general anaesthesia, most of the patients (46, 76.66%) preferred the technique over general anaesthesia while 15% of the dases thought that later would have been better. About 8% patients were of the view that either of the technique was equally good. (Table XII).

On a review of the above findings it can well be maintained that there is incontroversial evidence that intravenous regional centbucridine provides a uniform and adequate analgesia and anaesthesia in majority of the cases undergoing surgery under the technique. The optimal concentration as evidenced by the above findings can be .35%, as this concentration provides the best results,, a very suitable operating condition and has co mparatively low incidence of toxic reactions.

On the contrary although toxicity reactions are much less with .25% and .3% concentrations, but the analgesia produced is either incomplete or absent in majority of the cases, moreover the duration of effect is also very short and the patients required either repeat injection of the drug or supplementation by general anaesthetics. .4% concentration on the other hand no doubt produces 100% results but has the disadvantage of producing a very high (93%) incidence of toxicity reactions and is therefore not suitable.

# CONCLUSION

## CONCLUSIONS

With the study being completed on 60 patients, ranging between the ages of 11-70 yrs. of A.S.A. group I, operated upon under intravenous regional analgesia by centbucridine and after a careful review of the observations obtained the following salient conclusions are arrived at-

1- Intravenous regional analgesia is possible only in the extremities as the presence of continuous and uninterrupted tourniquet is an absolute requirement.

2. It is very safe and sure technique and can be employed for planned as well as the emergency operations.

3- The technique requires very little armamentarium and can suit field situations.

4. Premedication is not essential as a rule except in certain uncooperative and apprehensive emergency cases where sedation can be employed.

5. Depending upon the concentration of the drug used the patients were dividedinto 4 groups of 15 each. The concentrations used were .25,.30,.35 and .4%.

6. Centbucridine does not cause hypersensitivity reactions.

7. Exsanguination has been quite efficient by gravitational drainage, as evidenced by uniform analgesia and a bloodless operative field.

8. Tourniquet pain is not present if double cuff system is chosen.

9. The onset of action is extremely rapid and dose dependent taking only 1-2 minutes with .4% concentration of the drug to provide complete analgesia of the limb.

10. The dosage of 100-135 mg. are sufficient for producing adequate analgesia of the upper extremity and 190-240 mg for the lower extremity.

11. The ideal concentration of the drug to be used is .35%.

12. The degree of a analgesia and incidence of toxic reactions is directly proportional to the concentration of centbucridine solution used.

13. The cardiovascular stability is well marked and contrary to other conventional local analgesic drugs, it produces slight rise in blood pressure and respiratory rate.

14. Incidence of toxicity is very low. Mostly minor reactions were observed. Major toxicity reactions like venous thrombosis, one case, and gangrene, one case, was noticed with .4% concentration only.

15. The technique was liked by majority of patients (46, 76.66%). The bloodlessfield so achieved in the technique was highly appreciated by the surgeons.

16. There is no post anaesthetic discomfort.

Experience, skill and close attention are still the best adjuvants, coming a long way for the pinnacled success of the technique.

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